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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,694	ADAMS ET AL.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,164,485-512 and 515-520* is/are pending in the application.

4a) Of the above claim(s) *485-496,507 and 508* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,164,497-506 and 509-520* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Pursuant to the directives of the response filed 7/31/06, claims 13, 164, 497-500, 511, 512 have been amended. Claims 13, 164, 485-512, 515-520 remain now pending. Claims 497-500 are rejoined with the elected claims. Claims 485-496, 507, 508 are withdrawn from consideration, since they do not encompass the elected species. Claims 13, 164, 497-506, 509-520 are examined in this Office action.

The rejection of claims 511-512 under 35 U.S.C. 112, first paragraph (new matter) is withdrawn.

✦

35 U.S.C. §101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 164, 502, 504, 506, 510, 512, 514, 516, 518, 520 are rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

The cited claims are drawn to a method of "preventing" an infectious disease. This would mean that not a single virus, bacteria, fungus, parasite or prion can divide or propagate or

replicate while present within the subject. For example, suppose that one of the claimed compounds were administered to each of 1000 human subjects, and that each of those 1000 human subjects were were subjected to injections of HIV, influenza virus, anthrax, poxvirus, poliovirus, pneumococcus, and candida. Suppose that of those 1000 persons, 999 exhibited no adverse symptoms of any kind, but that the 1000th person developed a mild cold from which a recovered within a few days. Such a result would be wildly successful by any standard; yet such a result would actually constitute evidence that prevention had not been achieved. Applicants data does not come close to showing that prevention can be achieved.

In response to the foregoing, applicants have argued that one possible definition that might be applicable would be that which is found on page 79, line 1+, where the following phrase can be found:

"...resulting in a decrease in probability that the subject will develop the disorder"

The issue then is whether this suggestion supercedes the meaning that the skilled artisan would regard the term as encompassing. If it were really true that applicants have no interest in claiming "prevention", as this term is understood to the skilled artisan, applicants would feel no reluctance in amending the claim to recite *a method of reducing the probability that a subject will develop an infectious disease.* However, the reality is that applicants would prefer that the claims encompass "prevention", with all of its meanings and nuances.

Given applicants preference in this regard, maintaining this rejection is justified.

Claims 164, 502, 504, 506, 510, 512, 514, 516, 518, 520 are also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✦

Claims 13, 164, 497-506, 509-520 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown (p. 93) that administration of Ile-boroPro increases production of KC. From this, applicants are proposing that any and all infectious diseases can be successfully treated. Infectious diseases would include the following: Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid

Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, Yellow Fever. In addition, viral infections such as hepatitis and the flu would be included. Also, infections caused by endoparasites and fungi would be included.

There are principally three inquiries to be undertaken:

(a) is there even one "infectious disease" which can be successfully treated or prevented if a compound of claim 13 is administered prior to introduction of the infectious agent;

(b) in the event that there is in fact one "infectious disease" which can be successfully treated or prevented provided that a compound of claim 13 is administered prior to introduction of the infectious agent, does it follow therefrom that the majority of viral, bacterial, fungal, and endoparasitic infections can be successfully treated if a compound of claim 13 is administered prior to introduction of the infectious agent; and

(c) even if it is true that the majority of infectious diseases can be successfully treated if the compound of claim 13 is administered prior to introduction of the infectious agent, does it follow therefrom that such infectious diseases can be successfully treated if the compound of claim 13 is administered after the infectious disease has become firmly established.

Perhaps applicants will be able to point to a reference which shows that if KC or IL-8 is administered to a rat **before** the rat is infected with a specific bacteria or virus, the mortality rate will be lower as a result. However, this will not establish that any and all viral, bacterial, fungal, and endoparasitic infections can be successfully treated, even if the compound of claim 13 is administered prior to introduction of the infectious agent. Most importantly, even if it is true that the majority of infectious diseases can be

successfully treated if the compound of claim 13 is administered prior to introduction of the infectious agent, does it follow therefrom that such infectious diseases can be successfully treated if the compound of claim 13 is administered after the infectious disease is firmly established. For example, Wherry, John (*Journal of Virology* **79**(14), 8960-8, 2005) discloses that vaccination of mice with recombinant vaccinia virus was not particularly effective if the mice exhibited elevated viral loads of LCMV (lymphocytic choriomeningitis virus). In addition, Rupp, Richard (*Seminars in Pediatric Infectious Diseases* **16(1)**, 31-37, 2005) discloses that administration of a vaccine comprising truncated HSV-2 gD to HSV seronegative women provided a protective effect in some of the subjects, but was not effective in men, and was not effective in seropositive women. This result by Rupp supports the proposition that even if applicants could show that there exists an infectious disease for which efficacy can be achieved when the compound of claim 13 is administered before exposure to the infectious agent, "unpredictable" results will be obtained if applicants attempt to administer a compound of claim 13 after exposure to the infectious agent.

There is also the matter of "memory" effects. That is, suppose that a compound of claim 13 were administered to a rat several times over a period of e.g., 3 months, in a dosage that applicants would regard as optimal. Suppose that, subsequent to the last injection of the compound, a period of 10 days was allowed to pass before administering

a virus or bacteria (e.g., hepatits, salmonella, *P carnii*, or streptococcus). Would the compound be effective despite that lapse of 10 days from the last administration? If not, the claims would lack enablement on this basis alone, since the claims encompass any time lag between the last dosage of the compound, and exposure to the infectious agent.

The fact is that one cannot extrapolate from results obtained by administering KC or IL-8 prior to an infection, to a proposed therapy of an established infection. One cannot "predict" success in such a case. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Given the absence of working examples showing one how to treat an existing infection, and given the unpredictability in the art, the fact is that "undue experimentation" would be required to practice the claimed invention.

✦

Claim 13 is objected to on grammatical grounds. It would seem more appropriate to invert the phrase "effective amount" (i.e., to recite *amount effective to*).

✦

Claims 13, 164, 497-506, 509-520 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 13 is drawn to a method which calls for administering an "agent" of formula I. How is an "agent" different from a "compound"...? If a compound is intended, this should be made clear. A related issue is that the claim calls for administering an agent of formula I; according to the formula there is no carrier present. At the same time, however, the claim mandates that the agent is administered by injection or in an interically coated form. How do applicants propose to inject a solid compound? If a carrier is present, this should be made clear. (The same issues apply in the case of claim 164). In response, applicants have argued that there is an entry for the term "agent" in medical dictionaries. This particular point is undoubtedly true. This ground of rejection focuses on the fact that the term "agent" encompasses mixtures of compounds. In that respect, the claims are rendered indefinite. Applicants have offered only that they are hoping that examiners and potential practitioners of the invention will come to regard the term "agent" as limited to "compound". If this truly represents applicants' view on the matter, the issue can be laid to rest by using the term "compound" instead of agent.

- Claims 13 and 164 are indefinite as to the infectious diseases intended.

- Claim 13 makes reference to a variable "Am". This could be interpreted to mean that "m" is a subscript of "R", or that "R" is to be taken "m" times. Clarity would be enhanced by using the denotation $(A)_m$ instead of "Am". (The same issue applies in the case of claim 164).

- In the claims, the term "alphaketo" is indefinite. What is the keto group "alpha" to...? Is it an *alpha*-ketoamide, *alpha*-keto ester, *alpha*-keto phosphonate, *alpha*-keto boronic acid, *alpha*-keto acid, *alpha*-keto phosphate, or something else? In response, applicants have argued that the skilled artisan could glean from the specification those functional groups that are encompassed in addition to *alpha*-ketoamides, *alpha*-keto esters and *alpha*-keto acids. However, there is no evidence or indication that even applicants themselves could make such a

determination. If applicants themselves don't know what the term means, it seems unlikely that the skilled artisan would. If it is really true that the term at issue only encompasses *alpha*-ketoamides, *alpha*-keto esters and *alpha*-keto acids, applicants should feel no reluctance in using these terms, rather than a term that is vague and undefined.

- The claims recite the term "FAP". This term may be used if accompanied by an explanation of its meaning. Applicants are requested to explain what possible loss would be incurred by reciting the meaning of the term, in addition to the abbreviation.

- Claim 164 recites (last line) that the agent is present in the subject at a concentration above 10 nanomolar. However, it is unclear what this means. In particular, how does one calculate a "concentration" for bone? And in a tissue such as the heart or liver, how is concentration calculated; is the volume calculated on the basis of the entire organ or the liquid portion of it?

- Claims 511-512 make reference to agents in the plural, whereas in claim 1, "agent" is used only in the singular. Accordingly, "agents" (in the plural) lacks antecedent basis. In response, applicants have argued that when a person uses a term in the singular, he really intends for the plural to apply. The issue here is one of fundamental grammar and usage of the English language. The examiner maintains that applicants are incorrect in their analysis. There is in fact no indication in claim 13 or 164 that the composition comprises more than one agent. If there is descriptive support for it, applicants can add a claim which explicitly recites two or more agents.

✦

The following is a quotation of 35 USC. §103 which forms the basis for all obviousness rejections set forth in the Office action:

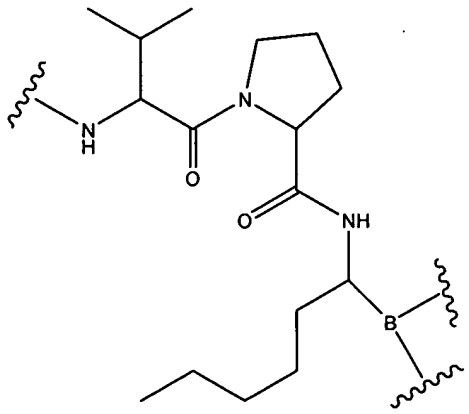
> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of

section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

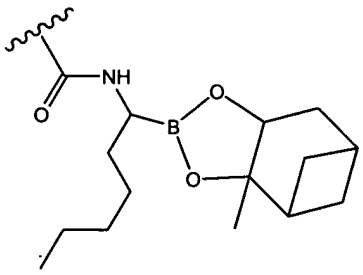
Claims 13, 164, 503-506, 509-520 are rejected under 35 U.S.C. §103 as being unpatentable over Priestley (USP 6,939,854).

As indicated previously, Priestley discloses various compounds in table 1 (col 64). Also disclosed is that the peptides can be used to treat hepatitis. Consider, for example, compound #35. This compound contains the following group:



As it happens, the following group qualifies as an "organoboronate" (two of the methyl groups

eliminated for simplicity):



The term at issue ("organoboronate") encompasses any group that contains carbon atoms and boron atoms.

Applicants have attempted to recast the issue into one of whether proline is an "obvious variant" or close structural homolog of valine. The examiner does not argue that proline is an "obvious variant" of valine. Rather, the examiner argues that valine qualifies as a close structural homolog of isoleucine, and that the claims are therefor rendered obvious.

The rejection is maintained.

✦

Claims 13 & 164 are rejected under 35 U.S.C. §103 as being unpatentable over Wallner (USP 6,355,614).

As indicated previously, Wallner discloses that the dipeptide Val-BoroPro can be used to

treat HIV infection. The term "prevention" is also recited at several locations.

In response to the foregoing, applicants have amended the claims to recite that the subject is HIV-negative. However, this ground of rejection is still valid insofar as the claims encompass "prevention". As a general proposition, when one endeavors to "prevent" a given disease, one administers a drug before the disease takes hold. If one is trying to prevent an HIV infection, one would administer the drug before any exposure to the virus has occurred. Thus, for the artisan of ordinary skill endeavoring to prevent HIV infection (in a subject who has not yet been exposed), the claims are still rendered obvious.

✦

Claims 13 & 164 are rejected under 35 U.S.C. §103 as being unpatentable over Wallner (USP 6,355,614) taken together with any of the following:

- Simons P (*AIDS (London, England)*, Vol. 11, No. 14, pp. 1783-4, 1997);
- Preiser W (*Journal of Medical Virology*, Vol. 60, No. 1, pp. 43-7, 2000);
- Giles R E (*Journal of Medical Virology*, Vol. 59, No. 1, pp. 104-9, 1999);
- Evans B. G., (*BMJ (Clinical Research ed.)*, Vol. 315, No. 7111, pp. 772-4, 1997);
- Zaaijer H L (*Journal of Medical Virology* 51(1), 80-82, 1997).

As indicated previously, Wallner discloses that the dipeptide Val-BoroPro can be used to treat HIV infection. Wallner does not disclose that attempts to ascertain the presence

of HIV (or antibodies thereto) in HIV-infected subjects will often produce a false negative result. Each of the secondary references discloses that false negative results often occur when HIV-infected subjects are tested.

The claims now recite that the subject must be "HIV-negative". The issue raised by this rejection is that the term "HIV-negative" would encompass those subjects who are indeed infected, but for whom the test is negative. As such, the phrase in question "HIV-negative" is not effective to exclude those subjects who have already been infected. Thus, the claims are rendered obvious.

✦

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON, PH.D.
PRIMARY EXAMINER